UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/925,122	08/08/2001	Olga Bandman	PF-0419-2 DIV	7383

27904 7590 12/19/2003

INCYTE CORPORATION (formerly known as Incyte Genomics, Inc.)
3160 PORTER DRIVE
PALO ALTO, CA 94304

EXAMINER	
HUYNH, PHUONG N	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 12/19/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/925,122	BANDMAN ET AL.	
	Examiner	Art Unit	
	Phuong Huynh	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *Three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 September 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *8 and 44-59* is/are pending in the application.

4a) Of the above claim(s) *44, 47, 49, 58 and 59 are* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *8,45,46,48 and 50-57* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Notice to comply.*

DETAILED ACTION

1. In view of the Appeal Brief filed on September 11, 2003, Prosecution is hereby reopened. New grounds of rejections are set forth below.

To avoid abandonment of the application, appellant must exercise one of the following two options:

(a) file a reply under 37 CFR 1.111 (if this Office action is non-final) or a reply under 37 CFR 1.113 (if this Office Action is final); or,

(b) request reinstatement of the appeal. If reinstatement of the appeal is requested, such request must be accompanied by a supplemental appeal brief, but no new amendments, affidavits (37 CFR 1.130, 1.131 or 1.132) or other evidence are permitted. See 37 CFR 1.193(b) (2).

2. Claims 8, and 44-59 are pending.

3. Claims 44, 47, 49, 58 and 59 stand withdrawn from further consideration by the examiner, 37 C.F.R. 1.142(b) as being drawn to non-elected inventions.

4. Claims 8, 45-46, 48 and 50-57 are being acted upon in this Office Action.

5. Claim 8 is objected for reciting non-elected embodiment, i.e., SEQ ID NO: 3.

6. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821 (a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 C.F.R. 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/or Amino Acid Sequence Disclosure.

The amino acid sequences disclosed on page 2, line 17 of the specification need to comply with the sequence rules. Appropriate correction is required.

7. 35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

8. Claims 8, 45-46, 48 and 50-57 are rejected under 35 U.S.C. 101 as the claimed invention is not supported by either a specific and substantial asserted utility or a well-established utility. Applicant is directed to the Final utility guideline published January 2001 and corresponding training materials (available on the PTO Website), none of the disclosed uses is a specific, credible and/or substantial use.

Claims 8, 45-46, 48 and 50-57 are drawn to an isolated antibody such as monoclonal antibody, polyclonal antibody, chimeric antibody, single chain, humanized antibody, antigen binding fragment thereof and labeled antibody thereof which "specifically binds" to a polypeptide comprising the amino acid sequence of SEQ ID NO: 1, wherein the antibody binds to any epitope of a polypeptide of SEQ ID NO: 1 or to a polypeptide comprising *any* "naturally occurring" amino acid sequence at least 90% to the amino acid sequence of SEQ ID NO: 1 wherein said antibody binds to any epitope of a polypeptide having a naturally occurring amino acid sequence at least 90% identical to SEQ IDNO: 1, said naturally occurring amino acid sequence having "HS3C activity". A composition comprising said polyclonal or monoclonal antibody and an acceptable excipient or suitable carrier. A method of making said antibody.

The specification discloses only a human SH3 containing protein (HS3C) comprising SEQ ID NO: 1 that shares 51% and 87% identity with HS3C-2 and mouse forming binding protein FBP17, respectively (page 15, line 17-19 of specification). The specification further discloses a method of making and using a polyclonal, monoclonal, chimeric, humanized antibody which specifically binds to a polypeptide consisting of an amino acid sequence of SEQ ID NO: 1 for diagnostic and detection assays (See page 31-32). At page 13 of the specification, the specification defines "specific binding" or "specifically binding" refers to interaction between a protein or peptide and an agonist, antibody and an antagonist. The interaction is dependent upon the presence of a particular structure, i.e., antigenic determinant or epitope of a protein recognized by the binding molecule. For example, if an antibody is specific for epitope "A", the presence of a protein containing epitope A (or free unlabeled A) in the reaction containing labeled "A" and the antibody will reduce the amount of labeled A bond to the antibody. However, the epitope to which the claimed antibody binds is not defined.

However, the claimed antibody is not supported by a specific asserted utility because the disclosed use(s) of the polypeptide such as a polypeptide comprising the amino acid sequence of SEQ ID NO: 1 or any naturally occurring amino acid sequence at least 90% identical to SEQ ID NO: 1 are not specific. Further, the HS3C activity is not clear. With regard to "HS3C activity",

the specification on page 54 states that HS3C activity is measured by binding of HS3C to radiolabeled formin polypeptide containing the proline-rich region. However, the HS3C activity is not specific to SEQ ID NO: 1 and is generally applicable to any polypeptide.

With regard to specific utility, the specification states on page 15 that the polypeptide of SEQ ID NO: 1 may be useful for diagnosis, prevention or treatment of various cancer, and immune and developmental disorders such as the ones on page 40 and useful to make antibody, etc. However, Northern analysis shows that the mRNA of polypeptide of SEQ ID NO: 1 is expressed 48% of cancerous tissue such as prostate tumor, immortalized cell line and inflammatory tissues, suggesting that the HS3C-1 (SEQ ID NO: 1) expression is not specific. (page 15, line 27-30, page 28, lines 3-5). The disclosure merely extends an invitation for further experimentation. Therefore the polypeptide having the amino acid sequence of SEQ ID NO: 1 or any naturally occurring amino acid at least 90% to the amino acid sequence of SEQ ID NO: 1 has no utility.

Similarly, the antibody to the polypeptide having the amino acid sequence of SEQ ID NO: 1 may be used for purification of any naturally occurring HS3C, may be use for identify molecules which interact with HS3C (page 55). These are non-specific uses that are applicable to any antibody in general and not particular or specific to antibody being claimed. Furthermore, the specification fails to provide objective evidence of any HS3C activity for the polypeptide of SEQ ID NO: 1 or any naturally occurring amino acid that is 90% identical to SEQ ID NO: 1 other than binding to formin protein (page 54) or to show that these proteins have function, or specific utility. Based on sequence homology to Scr protein, applicant asserts that the protein of SEQ ID NO: 1 and any naturally occurring variants thereof that is 90% identical to SEQ ID NO: 1 have potential phosphorylation sites and associated with various cancers, inflammatory tissues. However, a utility such as binding to proline rich sequence would apply to virtually every naturally occurring polypeptide and is therefore not specific to the polypeptide of SEQ ID NO: 1. Therefore the antibody that binds to a polypeptide having the amino acid sequence of SEQ ID NO: 1 or any naturally occurring amino acid at least 90% to the amino acid sequence of SEQ ID NO: 1 has no utility.

With regard to "naturally occurring" amino acid sequence that is at least 90% identical to the amino acid sequence of SEQ ID NO: 1, there is insufficient guidance as to which undisclosed polypeptide that is 90% identical to SEQ ID NO: 1 having a specific function or activity, much less to which epitope on the undisclosed "naturally occurring" variants of SEQ ID NO: 1 that the

claimed antibody binds. It is known that sequence with identity does not predict biological function. Attwood *et al* teach that protein function is context-dependent and the state of the art of making functional assignments merely on the basis of some degree of similarity between sequences and the current structure prediction methods is unreliable. Skolnick *et al.*, teach that squence-based methods for function prediction are inadequate and knowing a protein's structure does not necessary tell one it's function (See entire document, Abstract in particular). Until a specific function or activity of the polypeptide of SEQ ID NO: 1 and its naturally occurring variants thereof that is at least 90% identical to SEQ ID NO: 1 is identified and has a specific function, the said polypeptides have no utility. Since the polypeptide of SEQ ID NO: 1 and naturally occurring variant thereof lack a specific function or has any functional or biological activity, it follows that the antibody that binds to said polypeptides has no specific utility. As such, further research would be required. See Brenner v. Manson, 383 U.S. 519, 535-36, 148 USPQ 689, 696 (1966), the court indicates that "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion." A patent is therefore not a license to experiment.

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 8, 45-46, 48 and 50-57 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Since the claimed invention is not supported by a well established utility for the reasons set forth in the rejection under 35 USC 101 above, one skilled in the art clearly would not know how to use the claimed invention.

In addition, the specification fails to provide guidance as how to make *any* polypeptide comprising *any* "naturally-occurring" amino acid sequence having at least 90% sequence identity to the amino acid sequence of SEQ ID NO: 1 having HS3C activity and any antibody as set forth in claims 8, 45-46, 48 and 50-57.

The specification discloses only a human SH3 containing protein (HS3C) comprising SEQ ID NO: 1 that shares 51% and 87% identity with HS3C-2 and mouse forming binding protein FBP17, respectively (page 15, line 17-19 of specification). The specification further discloses only a method of making and using polyclonal, monoclonal, chimeric, humanized antibody which specifically binds to a polypeptide comprising SEQ ID NO: 1 wherein the antibody is a chimeric antibody, a single chain antibody, a Fab fragment, a F(ab')2 fragment thereof or a humanized antibody for diagnostic and detection assays (See page 31-32). The specification discloses HS3C activity as measuring the binding of HS3C to radio labeled formin polypeptides containing the proline-rich region (See page 54 at lines 19-21, in particular).

However, the specification does not teach how to make *any* polypeptide "having a naturally occurring amino acid sequence at least 90% identical to SEQ ID NO: 1" having a specific function as the polypeptide comprising SEQ ID NO: 1, much less the about the binding specificity of the claimed antibody. There is sufficient guidance as the antigenic determinant (i.e. the specific amino acid sequence of the immunogen or polypeptide fragment) used by applicant to make any antibody mentioned above that binds to *any* "epitope" of a polypeptide of SEQ ID NO: 1 or *any* "epitope" of a polypeptide having 10% difference (90% identity) in the amino acid sequence of SEQ ID NO:1, which is equivalent to having 26-27 amino acid difference in SEQ ID NO: 1. Further, the term comprising or having is open-ended. It expands the "immunogenic fragment" to include additional amino acids at either or both ends. There is insufficient guidance as to the undisclosed amino acid added to the immunogenic fragment for making antibody that binds to the full-length polypeptide of SEQ ID NO: 1 or any polypeptide having 10% difference in the amino acid sequence of SEQ ID NO:1, which is equivalent to having 26-27 amino acid difference in SEQ ID NO: 1, or any epitope of said polypeptides. Further, there are no working examples in the specification as filed that the claimed antibody ever been made, much less demonstrating the binding specificity of the claimed antibody, in turn, would be useful for diagnosis of any disease where the polypeptide of SEQ ID NO: 1 is expressed only 48% in tumor or inflammatory tissues.

Kuby *et al*, of record, teach that antibody epitopes (B cell epitopes) are not linear and are comprised of complex three-dimensional array of scattered residues which will fold into specific conformation that contribute to binding (See Kuby 1994, page 94, in particular). Immunization with a peptide fragment may result in **antibody specificity** that differs from the antibody specificity directed against the native full-length polypeptide.

Abaza *et al* teach that even a single amino acid substitution outside the antigenic site can exert drastic effects on the reactivity of a protein with monoclonal antibody against the site (See abstract, in particular). Without the specific amino acid residues of the immunogen used by applicant, it is unpredictable to determine which antibody generated from any immunogenic fragment having additional undisclosed amino acid would binds specifically to a polypeptide of SEQ ID NO: 1, a polypeptide comprising a naturally-occurring amino acid sequence such as having 90% sequence identity to SEQ ID NO: 1 wherein the naturally occurring amino acid sequence binds having "HS3C activity" or *any* epitope of a polypeptide of SEQ ID NO: 1 or any epitope of a polypeptide comprising a naturally-occurring amino acid sequence such as having 90% sequence identity to SEQ ID NO: 1 wherein the naturally occurring amino acid sequence binds having "HS3C activity".

With regard to "HS3C activity", the specification discloses HS3C activity as measuring the binding of HS3C to the proline-rich region of a radiolabeled formin polypeptides that interacts with the SH3 containing protein (See page 54 at lines 19-21, in particular). However, binding does not equal to functions since any polypeptide can bind to any proline-rich region of the formin polypeptide, much less a polypeptide having 90% sequence identity to SEQ ID NO: 1 or 26-27 amino acid difference to SEQ ID NO: 1.

Ngo *et al* teach that the amino acid positions within the polypeptide/protein that can tolerate change such as conservative substitution or no substitution, addition or deletion which are critical to maintain the protein's structure/function will require guidance (see Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495).

Skolnick *et al* teach that sequence-based methods for function prediction are inadequate and knowing a protein's structure does not tell one its function (See abstract, in particular).

It is known in the art that even a single amino acid difference in a polypeptide would produce antibody that fails to bind to said polypeptide. Since the amino acid sequence of the immunogen used by applicant and/or the binding specificity of said antibody are not disclosed, it follows that the method of making the antibody that binds to any naturally occurring variants of SEQ ID NO: 1 is not enabled.

With regard to composition comprising *any* polyclonal or monoclonal antibody with the specificity mentioned above and an acceptable excipient or suitable carrier, the specification fails to provide any *in vivo* working examples, or guidance with respect to treating a patient suffering from *any* specific disease using *any* antibody mentioned above. Given the indefinite number of

undisclosed disease or conditions that may or may not associated with the expression of "HS3C" and the lack of guidance as to the function of SEQ ID NO: 1 or a polypeptide having a naturally occurring amino acid sequence at least 90% identical to SEQ ID NO: 1 having binding activity to the proline-rich region of a radiolabeled forming polypeptide that binds to SH3 domain containing proteins, further research is required. Since the composition comprising said antibody is not enabled, it follows that composition comprising the labeled antibody is not enabled.

The '370 patent teaches that the inherent problem with chimeric antibody has been a loss of affinity for the antigen, which means more antibody will have to be injected into a patient at higher cost and greater risk of adverse effects such as serum sickness (See column 2 lines 12-27, in particular). In the absence of in vivo working examples, it is unpredictable for the following reasons: (1) the antibody may be inactivated before producing an effect, i.e. such as inherently short half-life of the antibody; (2) the antibody may not reach the target area; and (3) other functional properties, known or unknown, may make the antibody unsuitable for *in vivo* therapeutic use, i.e. such as serum sickness which prohibitive to the use of antibody for such treatment. Therefore, it would require undue experimentation of one skilled in the art to practice the claimed invention. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

11. Claims 8, 45-46, 48 and 50-57 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The specification does not reasonably provide a **written description** of *any* antibody which "specifically binds" to any "naturally occurring" amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO: 1, wherein the antibody binds to any epitope of any polypeptide having a "naturally occurring" amino acid sequence at lest 90% identical to SEQ ID NO: 1, said naturally occurring amino acid sequence having "HS3C activity" as set forth in claims 8, 45-46, 48 and 50-57.

The specification discloses only a human SH3 containing protein (HS3C) comprising SEQ ID NO: 1 that shares 51% and 87% identity with HS3C-2 and mouse forming binding protein FBP17, respectively (page 15, line 17-19 of specification). The specification further discloses only a method of making and using polyclonal, monoclonal, chimeric, humanized

antibody which specifically binds to a polypeptide comprising SEQ ID NO: 1 for diagnostic and detection assays (See page 31-32). The specification discloses HS3C activity as measuring the binding of HS3C to radio labeled formin polypeptides containing the proline-rich region (See page 54 at lines 19-21, in particular). At page 13 of the specification, the specification defines "specific binding" or "specifically binding" refers to interaction between a protein or peptide and an agonist, antibody and an antagonist. The interaction is dependent upon the presence of a particular structure, i.e., antigenic determinant or epitope of a protein recognized by the binding molecule. For example, if an antibody is specific for epitope "A", the presence of a protein containing epitope A (or free unlabeled A) in the reaction containing labeled "A" and the antibody will reduce the amount of labeled A bond to the antibody. However, the epitope to which the claimed antibody binds is not defined.

Other than the specific polypeptide comprising SEQ ID NO: 1, there is inadequate written description about the structure such as the amino acid sequence of any "naturally occurring" variants of SEQ ID NO: 1 that is 90% identical to SEQ ID NO: 1 having a specific function or a specific activity. Further, there is inadequate written description about the binding specificity of the claimed antibody. The claimed antibody binds to any undisclosed polypeptide that is found in nature having an amino acid that is at least 90% identical to SEQ ID NO: 1, which is drawn to a genus of undisclosed polypeptide, that is not taught in the specification. A 90% identity to SEQ ID NO: 1 means 10% difference, which is equivalent to having 26-27 amino acids difference (SEQ ID NO 1 which has 265 amino acids and multiply that by 10%). Given the indefinite number of undisclosed naturally occurring amino acid sequence that is at least 90% identical to SEQ ID NO: 1, the polypeptide having a naturally occurring amino acid at least 90% identical to SEQ ID NO: 1 is not adequately described. Since the naturally occurring variants of SEQ ID NO: 1 is not adequately described, it follows that the antibody that binds to the undisclosed naturally occurring variant of SEQ ID NO: 1 is not adequately described.

Further, given the lack of written description about epitope to which the claimed antibody binds, the binding specificity of the claimed antibody such as monoclonal, polyclonal, chimeric, humanized and antigen binding fragment thereof is not adequately described.

With regard to HSC3 activity, the specification on page 54 states that HS3C activity is measured by binding of HS3C to radiolabeled formin polypeptide containing the proline-rich region. However, the HS3C activity is not a specific to SEQ ID NO: 1 and is generally applicable to any polypeptide. Therefore, the specific function of a polypeptide comprising the amino acid

sequence of SEQ ID NO: 1 or any polypeptide comprising any naturally occurring amino acid sequence at least 90% identical to SEQ ID NO: 1 is not adequately described.

Finally, the specification discloses only two polypeptides comprising SEQ ID NO: 1 (species) and SEQ ID NO: 3 from human and mouse, respectively. Given the lack of a written description of *any* additional representative species of polypeptide comprising a "naturally occurring" amino acid sequence at least 90% identical to SEQ ID NO: 1 as encompassed by the claimed antibody to which it binds, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.*

Applicant is directed to the Final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

12. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

13. Claims 46 and 48 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The "antibody is labeled" in claim 48 has no antecedent basis in base claim 8. It is suggested that claim 48 be rewritten as "A composition comprising a labeled antibody wherein the antibody of claim 8 is labeled". It is also suggested that claim 46 be rewritten as "A composition comprising **the** antibody of claim 8 and an acceptable excipient".

14. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

15. This application currently names joint inventors. In considering Patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

16. Claims 8 and 50-52 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chan *et al* (EMBO J 15(5): 1045-54, 1996; PTO 892) in view of Harlow *et al* (in Antibodies a Laboratory Manual, 1988, Cold Spring harbor laboratory publication, Cold Spring Harbor, NY, pages 29, 33 and 93).

Chan *et al* teach a polypeptide such as forming binding protein FBP17 that has various long stretch of amino acid residues that are identical to the claimed SEQ ID NO: 1 such as TCP to PTSYV (See Figure 3A, in particular) and as is evidenced by the sequence alignment accompanied by the appeal brief (865744 and FBP). The reference polypeptide is an immunogenic fragment of the claimed polypeptide of SEQ ID NO: 1 and is also a naturally occurring amino acid sequence that is at least 90% identical to the claimed biologically active or immunogenic fragment polypeptide of SEQ ID NO: 1 (residues 198-244 of SEQ ID NO: 1) (See Fig 3A, in particular). Chan *et al* teach a biologically active or immunogenic fragment such as APPTPPPLPP (page 1046, Fig 1, 1048, column 1, first paragraph, in particular) and the reference fragment is functionally resembles SH3 domain, which is useful for regulating limb and kidney development (See page 1045, in particular). Further, Chan *et al* teach that antibodies to various binding forming protein such as antibodies to FBP21 or FBP11 or FBP28 are useful for detection assays (See page 1049, caption of Figure 5, in particular).

The claimed invention in claim 8 differs from the teachings of the reference only that an isolated antibody specifically binds to an epitope of a polypeptide comprising an amino acid sequence of SEQ ID NO: 1 or to an epitope of a polypeptide having a naturally occurring amino acid sequence at least 90% identical to SEQ ID NO: 1.

The claimed invention in claim 50 differs from the teachings of the reference only that a method of preparing a polyclonal antibody with the specificity of the antibody of claim 8, the method comprises: immunizing an animal with an immunogenic fragment of SEQ ID NO: 1

under conditions to elicit an antibody response, isolating antibodies from said animal and screening the isolated antibodies that binds to a polypeptide having an amino acid sequence of SEQ ID NO: 1.

The claimed invention in claim 52 differs from the teachings of the reference only by the recitation that a composition comprising a polyclonal antibody with the specificity mentioned above and a suitable carrier.

Harlow *et al* teach a method of producing polyclonal antibodies to any antigen by immunizing an animal such as rabbit, or goat with any peptide conjugated to KLH (See page 93, in particular) and that polyclonal antibodies are useful for many types of immunoassays because polyclonal antibodies bind to several antigenic determinants on a protein and cross react with common determinants that provides an excellent target for identify two proteins which have similar determinants (See page 29, and 33, in particular) and polyclonal antibody produced are well characterized and easily purified (page 93). Harlow *et al* teach a composition comprising an antibody and a carrier such as PBS (See page 354, in particular) or NaCl, which is a saline solution (See page 346, in particular) for various detection assays.

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to produce polyclonal antibody as taught by Harlow *et al* by immunizing an animal with the immunogenic fragment such as residues TCP to PTSYV of FBP17 or the full length reference polypeptide as taught by Chan *et al,* isolating the antibodies from the animal by screening antibodies that binds to forming binding protein for a composition comprising an antibody and a carrier for detection assay as taught by Harlow *et al*. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because Harlow *et al* teach that polyclonal antibodies are useful for many types of immunoassays because polyclonal antibodies bind to several antigenic determinants on an antigen and cross react with common determinants that provides an excellent target for identify two proteins which have similar determinants (See page 29, and 33, in particular) and polyclonal antibody produced are well characterized and easily purified (page 93). Chan *et al* teach that antibodies to forming binding protein such as FBP21 or FBP11 or FBP28 are useful for detection assays (See page 1049, caption of Figure 5, in particular).

17. Claims 8, 45, 46 and 48 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chan *et al* (EMBO J 15(5): 1045-54, 1996; PTO 892) in view of Harlow *et al* (in Antibodies a Laboratory Manual, 1988, Cold Spring harbor laboratory publication, Cold Spring Harbor, NY, pages 319-356, and 626-629).

The teachings of Chan *et al* have been discussed supra.

The claimed invention in claim 45 differs from the teaching of the reference only that the antibody is a Fab fragment, an F(ab')2 fragment.

The claimed invention in claim 46 differs from the teaching of the reference only that a composition comprising an antibody which specifically binds to an epitope of a polypeptide comprising the amino acid sequence of SEQ ID NO: 1 or an epitope of a polypeptide having a naturally occurring amino acid sequence at least 90% identical to SEQ ID NO: 1 having HS3C activity and an acceptable excipient.

The claimed invention in claim 48 differs from the reference only that antibody which specifically binds to an epitope of a polypeptide comprising the amino acid sequence of SEQ ID NO: 1 or an epitope of a polypeptide having a naturally occurring amino acid sequence at least 90% identical to SEQ ID NO: 1 having HS3C activity is labeled.

Harlow *et al* teach a method of producing antibody fragment wherein the fragment is Fab or F(ab')2 fragment (See page 626-629, in particular). Harlow *et al* teach that the problems of using multivalent antibodies on mammalian cells often will lead to capping and internalization of the antigen which can be overcome by using fragments of antibodies (See page 626 in particular). Harlow *et al* further teach labeling any antibody with various labels such as enzyme or FITC (See chapter 9, in particular) in a composition comprising an antibody and a carrier such as PBS (See page 354, in particular) or NaCl, which is a saline solution (See page 346, in particular) for various detection assays. The advantages of enzyme labeling are longer shelf life, and higher sensitivity while the advantages of fluorochrome label are long shelf life and good resolution in immunohistochemistry (See page 322, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to produce antibody fragment such as Fab or F(ab')2 or to label any antibody as taught by Harlow *et al* with the polyclonal antibody that binds specific to the polypeptide that has an epitope identical to the claimed polypeptide comprising SEQ ID NO: 1 or a naturally occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO: 1 and has HS3C activity as taught by Chan *et al*. From the combined teachings of the references,

it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because Harlow *et al* teach antibody fragments can overcome the problem of capping and internalization of the antigen on mammalian cell when using multivalent antibodies (See page 626 in particular) and the labeled antibody can be used for various detection assays. The advantages of enzyme labeling are longer shelf life, higher sensitivity while the advantages of fluorochrome label are long shelf life and good resolution in immunohistochemistry (See page 322, in particular). Claim 8 is included in this rejection because said claim provides antecedent basis for the antibody fragment such as Fab fragment and F(ab')2 fragment.

18. Claim 45 is rejected under 35 U.S.C. 103(a) as being unpatentable over Chan *et al* (EMBO J 15(5): 1045-54, 1996; PTO 892) in view of Harlow *et al* (in Antibodies a Laboratory Manual, 1988, Cold Spring harbor laboratory publication, Cold Spring Harbor, NY, pages 29, 33 and 93) as applied to claims 8 and 50-52 and further in view of US Pat No. 4,946,778 (Aug 1990, PTO 892).

The combined teachings of Chan *et al* and Harlow *et al* have been discussed supra.

The claimed invention in claim 45 differs from the reference only by the recitation that the antibody is a single chain antibody.

The '778 patent teaches a method of producing single chain antibody comprising a variable region of any antibody (See column 29, lines 25 bridging column 30, lines 1-20, in particular). The advantages of a single chain antibody are small size, greater stability, significantly reduced cost and could be engineered to be highly antigenic and yet reduce the body's immunologic reaction and thus increase the safety and efficacy of the therapeutic application (See column 3, lines 33-48, in particular).

Therefore, it would have been obvious to one having ordinary skill in the art at the time the invention was made to make single chain antibody as taught by the '778 patent from antibody as taught by Harlow et al that binds to the polypeptide that has an epitope identical to the claimed polypeptide comprising SEQ ID NO: 1 or a naturally occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO: 1 and has HS3C activity as taught by Chan *et al*. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art at the time the invention was made would have been motivated to do this because the '778 patent teaches the advantages of a single chain antibody are small size, greater stability, significantly reduced cost and could be engineered to be highly antigenic and yet reduce the body's immunologic reaction and thus increase the safety and efficacy of the therapeutic application (See column 3, lines 33-48, in particular).

19. Claim 45 is rejected under 35 U.S.C. 103(a) as being unpatentable over Chan *et al* (EMBO J 15(5): 1045-54, 1996; PTO 892) in view of US Pat No. 4,946,778 (Aug 1990, PTO 892).

The teachings of Chan *et al* have been discussed supra.

The claimed invention in claim 45 differs from the reference only by the recitation that the antibody is a single chain antibody.

The '778 patent teaches a method of producing single chain antibody from polypeptide fragment (See column 29, lines 25 bridging column 30, lines 1-20, in particular). The advantages of a single chain antibody are small size, greater stability, significantly reduced cost and could be engineered to be highly antigenic and yet reduce the body's immunologic reaction and thus increase the safety and efficacy of the therapeutic application (See column 3, lines 33-48, in particular).

Therefore, it would have been obvious to one having ordinary skill in the art at the time the invention was made to make single chain antibody as taught by the '778 patent that binds to the polypeptide that has an epitope identical to the claimed polypeptide comprising SEQ ID NO: 1 or a naturally occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO: 1 and has HS3C activity as taught by Chan *et al*. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art at the time the invention was made would have been motivated to do this because the '778 patent teaches the advantages of a single chain antibody are small size, greater stability, significantly reduced cost and could be engineered to be highly antigenic and yet reduce the body's immunologic reaction and thus increase the safety and efficacy of the therapeutic application (See column 3, lines 33-48, in particular).

20. Claims 45, 56 and 57 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chan *et al* (EMBO J 15(5): 1045-54, 1996; PTO 892) in view of US Pat No. 6,180,370B, filed June 1995; PTO 892).

The teachings of Chan *et al* have been discussed supra.

The claimed invention in claim 45 differs from the reference only by the recitation that the antibody is a chimeric antibody, a humanized antibody which bind to an epitope of a polypeptide of SEQ ID NO: 1 or to an epitope of a polypeptide comprising a naturally occurring variant thereof, the variant being at least 90% identical to SEQ ID NO: 1 and having HS3C activity.

The claimed invention in claim 56 differs from the teachings of the reference only that the antibody is produced by screening a Fab expression library.

The claimed invention in claim 57 differs from the teachings of the reference only that the antibody is produced by screening a recombinant immunoglobulin library.

The '370 patent teaches a method of producing chimeric antibodies (See column 55 lines 25-59; column 59, lines 65, in particular) and humanized antibodies (See column 44 line 33; column 68 lines 8-44, in particular) by screening a Fab expression library or a recombinant immunoglobulin library. The reference chimeric antibody comprising a variable region of an antibody and a human immunoglobulin constant region. The '370 patent further teaches that the chimeric humanized immunoglobulins (antibodies) specifically reactive with strong affinity to a predetermined antigen and remain nonimmunogenic in humans yet be easily and economically produced in a manner suitable for therapeutic formulation and other uses (See column 2, lines 29-34, in particular).

Therefore, it would be been obvious to one having ordinary skill in the art at the time the invention was made to produce chimeric antibody or humanized antibody as taught by the '370 patent that binds specifically binds to the polypeptide that has an epitope identical to the claimed polypeptide comprising SEQ ID NO: 1 or a naturally occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO: 1 and has HS3C activity as taught by Chan *et al*. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art at the time the invention was made would have been motivated to do this because the '370 patent teaches that the chimeric humanized immunoglobulins (antibodies) specifically reactive with strong affinity to a predetermined antigen

and remain nonimmunogenic in humans yet be easily and economically produced in a manner suitable for therapeutic formulation and other uses (See column 2, lines 29-34, in particular).

21. Claims 53-55 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chan *et al* (EMBO J 15(5): 1045-54, 1996; PTO 892) in view of Harlow *et al* (in Antibodies a Laboratory Manual, 1988, Cold Spring harbor laboratory publication, Cold Spring Harbor, NY, pages 139-149).

The teachings of Chan et al have been discussed supra.

The claimed invention in claim 53 differs from the teachings of the reference only by the recitation that a method of making monoclonal antibody comprising immunizing an animal with an immunogenic fragment of a polypeptide of SEQ ID NO: 1, isolating antibody producing cells from the animal, fusing the antibody producing cells with immortalized cells to form monoclonal antibody producing hybridoma cells, culturing the hybridoma cells and isolating antibody which bind to an epitope of a polypeptide of SEQ ID NO: 1 or to an epitope of a polypeptide comprising a naturally occurring variant thereof, the variant being at least 90% identical to SEQ ID NO: 1 and having HS3C activity.

The claimed invention in claim 54 differs from the teachings of the reference only by the recitation that a monoclonal antibody produced by the method of immunizing an animal with an immunogenic fragment of a polypeptide of SEQ ID NO: 1, isolating antibody producing cells from the animal, fusing the antibody producing cells with immortalized cells to form monoclonal antibody producing hybridoma cells, culturing the hybridoma cells and isolating antibody which bind to an epitope of a polypeptide of SEQ ID NO: 1 or to an epitope of a polypeptide comprising a naturally occurring variant thereof, the variant being at least 90% identical to SEQ ID NO: 1 and having HS3C activity.

The claimed invention in claim 54 differs from the teachings of the reference only by the recitation that a composition comprising said monoclonal antibody and a suitable carrier.

Harlow *et al* teach a method of producing monoclonal antibody comprising immunizing an animal with an immunogenic fragment of a polypeptide of interested, isolating antibody producing cells from the animal, fusing the antibody producing cells with immortalized cells to form monoclonal antibody producing hybridoma cells, culturing the hybridoma cells and isolating antibody which bind to the polypeptide of interested (See page 139-149, in particular). Harlow et al teach that the advantages of monoclonal antibodies are their specificity of binding, their homogeneity and their ability to be produced in unlimited quantities (See page 141, last full

paragraph, in particular). Harlow *et al* further teach labeling any antibody with various labels such as enzyme or FITC (See chapter 9, in particular) in a composition comprising an antibody and a carrier such as PBS (See page 354 in particular) or NaCl, which is a saline solution (See page 346) for various detection assays. The advantages of enzyme labeling are longer shelf life, higher sensitivity while the advantages of fluorochrome label are long shelf life and good resolution in immunohistochemistry (See page 322, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to produce monoclonal antibody as taught by Harlow et al that binds to the polypeptide that has an epitope identical to the claimed polypeptide comprising SEQ ID NO: 1 or a naturally occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO: 1 and has HS3C activity as taught by Chan *et al* for a composition comprising said antibody and a carrier such as PBS for detection assay as taught by Chan et al or Harlow *et al.* From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to make antibody fragment because Harlow *et al* teach that the advantages of monoclonal antibodies are their specificity of binding, their homogeneity and their ability to be produced in unlimited quantities (See page 141, last full paragraph, in particular). Chan *et al* teach that antibodies to forming binding protein are useful for detection assays (See page 1049, caption of Figure 5, in particular).

22. No claim is allowed.

23. Any inquiry concerning this communication or earlier communications from the examiner should be directed to "Neon" Phuong Huynh whose telephone number is (703) 308-4844. The examiner can normally be reached Monday through Friday from 9:00 am to 6:00 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist (customer service) whose telephone number is (703) 872-9305.

24. Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-7401. The IFW official Fax number is (703) 872-9306. For After Final, the Fax number is (703) 872-9307.

Phuong N. Huynh, Ph.D.
Patent Examiner
Technology Center 1600
December 15, 2003

CHRISTINA CHAN
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

JASEMINE C. CHAMBERS
DIRECTOR
TECHNOLOGY CENTER 1600